activity comprising administering to a mammal an oligoheteropolysaccharide comprising depolymerized heparin having an average molecular weight of about 2600 to about 5500 daltons determined by the Somogy method in comparison with commercial heparin and having sulfate groups in the quantity and in the positions characteristic of heparin, which oligoheteropolysaccharide displays greater antithrombotic activity than anticoagulant activity.

REMARKS

The amendments above were not submitted earlier because it was thought that the new claim 13 and the amended claims 10 and 11 which were submitted to the examiner on July 6, 1987 would be acceptable. In addition, the undersigned was appointed as attorney only one month ago, on November 9, 1987 (see the "Revocation of Power of Attorney and Appointment of New Attorney" which is enclosed).

The examiner stated that the expressions "more particularly" and "and following" in claim 10 should be deleted. Accordingly claim 10 has been amended to delete these expressions.

The examiner stated that the expression "lightly" in claim 11 should be "slightly". Accordingly claim 10 has been amended to delete this expression.

The examiner stated in an interview on August 14, 1987 that "method of use claims can possibly be allowed if clear and convincing unexpected results are shown employing the fragments in place of those of the prior art". Accordingly claims 10, 11 and 13 have been amended to become method of use claims. Claim 12 has been canceled without prejudice and essentially incorporated into claim 10. Clear and convincing unexpected results are shown employing the fragments of the invention and are shown in the Holmer "Declaration under rule 132" which is attached. Said declaration is discussed at length below.

Claims 10 to 13 were rejected under 35 U.S.C. 103 as being unpatentable over the British patent and Hladovec et al in view of Nader et al, Waldman et al and Thrombosis. Enclosed is a "Declaration under rule 132" from E. B. Holmer who is a co-author of the Thrombosis article cited by the examiner. Dr. Holmer examined an oligoheteropolysaccharide of the applicants' invention having a molecular weight of 4900. It exhibited an anti-Xa to APTT ratio of 1.86. As pointed out by Dr. Holmer, the Thrombosis article gives and anti-Xa to APTT ratio of approximately 20 for a fraction isolated from heparin having approximately the same molecular weight (a 5000 molecular weight heparin fraction obtained by gel filtration). These results are clear and convincing as well as unexpected. Clearly, applicants' product does not possess the same properties as the prior art

material. It is respectively submitted that in light of the Holmer declaration, the Thrombosis article is not relevant prior art especially with regard to the method claims now presented to the examiner.

It is respectfully submitted that the Hladovic et al reference is not relevant with regard to the method claims now presented to the examiner. Hladovec et al is concerned only with antilipemic activity which is totally unrelated to applicants' claims as they now stand. In addition Hladovic et al presents no experimental data with regard to the procedure for preparing or obtaining any of the compounds mentioned in said article making it impossible for one skilled in the art to practice anything mentioned in the Hladovic article.

With regard to the Nader et al article, the Waldman et al article and the British patent, it is respectfully submitted that these are conflicting and would confuse one skilled in the art rather than allow one skilled in the art to practice applicant's invention. This is particularly true in light of the fact that applicant's claims are now all methods claims. The British patent states that sulfation of low sulfate heparinoids increases the anticoagulant activity. See for example page 2 column 1 lines 38-44. The Nader et al article on page 506 discusses the anticoagulant differences between "heparitin sulfates A and B" and "heparitin sulfate D and heparin". The former two substances

are devoid of anticoagulant activity. It is pointed out that said former two substances "exhibit a lower degree of sulfation and the presence of N-acetyl groups".

On the other hand the Waldman et al article states that the sulfation process does not increase anticoagulant active. For example, page 1 of the Waldman et al article in the summary states that "partial resulfation of amino groups of inactive desulfated heparin restores heparin's protein-synthesis inhibitory ability almost completely, **WHILE NEGLIGIBLE ANTICOAGULANT ACTIVITY IS RESTORED**" (emphasis added).

Thus it is respectfully submitted that applicants' invention AS NOW CLAIMED is not unpatentable over the British patent, Hladovec et al, Nader et al, Waldman et al and Thrombosis under 35 U.S.C. 103.

The examiner states that "from page 4 (lines 13-18) of the specification, it is noted that the instant fragments are old and well known in the art. Applicant's respectfully point out lines 19-22 on the same page. "Such fractions, having a mol wt of 5,000 and containing variable amounts of sulfuric groups, generally less numerous than in heparin, have not found any useful therapeutic application heretofore". It is respectfully submitted that lines 13-18 do not adversely affect the patentability under 35. U.S.C. 103 and that in any event lines 19-22 demonstrate patentability.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Respectfully submitted,

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Kevin M. Foley, Attorney
Registration No. 31,507
Hepar Industries, Inc.
P.O. Box 338
Franklin, Ohio 45005
513-746-3603